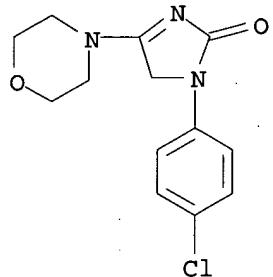


L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 188116-07-6 REGISTRY
ED Entered STN: 10 Apr 1997
CN 2H-Imidazol-2-one, 1-(4-chlorophenyl)-1,5-dihydro-4-(4-morpholinyl)- (9CI)
(CA INDEX NAME)
OTHER NAMES:
CN AWD 131-138
MF C13 H14 Cl N3 O2
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, EMBASE,
IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, PHAR, PROUSDDR, SCISEARCH,
SYNTHLINE, TOXCENTER, USPATFULL



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10 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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| COST IN U.S. DOLLARS | | ENTRY | SESSION |
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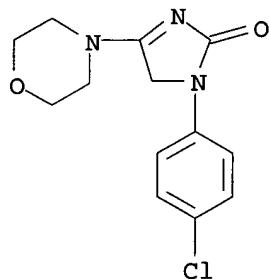
=> E "AWD 131-138"/CN 25
E1 1 AWD 122-60/CN
E2 1 AWD 123-281/CN
E3 1 --> AWD 131-138/CN
E4 1 AWD 140-076/CN
E5 1 AWD 140-190/CN
E6 1 AWD 160-275/CN
E7 1 AWD 19-166/CN
E8 1 AWD 21-360/CN
E9 1 AWD 23-111/CN
E10 1 AWD 23-115/CN
E11 1 AWD 23-15/CN
E12 1 AWD 26-06/CN
E13 1 AWD 33-173/CN
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E24 1 AWD 52-365/CN
E25 1 AWD 52-365 BITARTRATE/CN

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L1 1 "AWD 131-138"/CN

=> DIS L1 1 IDE
THE ESTIMATED COST FOR THIS REQUEST IS 1.95 U.S. DOLLARS

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L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 188116-07-6 REGISTRY
ED Entered STN: 10 Apr 1997
CN 2H-Imidazol-2-one, 1-(4-chlorophenyl)-1,5-dihydro-4-(4-morpholinyl)- (9CI)
(CA INDEX NAME)
OTHER NAMES:
CN AWD 131-138
MF C13 H14 Cl N3 O2
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, EMBASE,
IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, PHAR, PROUSDDR, SCISEARCH,
SYNTHLINE, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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10 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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| COST IN U.S. DOLLARS | | |
| FULL ESTIMATED COST | 8.70 | 8.91 |

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=> s 188116-07-6 or AWD 131-138

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L3

10 L2

184 AWD
12 AWDS
196 AWD
(AWD OR AWDS)

46127 131
44976 138
9 AWD 131-138
(AWD(W)131(W)138)

L4

14 L3 OR AWD 131-138

=> d ti au abs so py 1-14

L4 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN

TI Synthesis, Pharmacology, and Structure-Activity Relationships of Novel Imidazolones and Pyrrolones as Modulators of GABAA Receptors

AU Grunwald, Christian; Rundfeldt, Chris; Lankau, Hans-Joachim; Arnold, Thomas; Hoefgen, Norbert; Dost, Rita; Egerland, Ute; Hofmann, Hans-Joerg; Unverferth, Klaus

AB New series of imidazolones and pyrrolones were synthesized. The compds. were tested for their anxiolytic properties due to modulation of the GABAA receptor response. Several derivs. exhibit considerable pharmacol. activity while lacking the typical side effects of benzodiazepine receptor agonists. 1-(4-Chlorophenyl)-4-morpholin-1-yl-1,5-dihydro-imidazol-2-one and 1-(4-chlorophenyl)-4-piperidin-1-yl-1,5-dihydro-imidazol-2-one were protective in the pentylenetetrazole test in rats with oral ED₅₀ of 27.4 and 12.8 mg/kg and TD₅₀ (rotarod) of >500 and 265 mg/kg, resp. The min. ED in the Vogel conflict test was 3 mg/kg for both compds. Common structure-activity relationship and comparative mol. field anal. models of the various series of derivs. could be established which are in accordance with a GABAA mediated pharmacol. action. The findings fit well into an established pharmacophore model. This model is refined by an addnl. steric restriction feature.

SO Journal of Medicinal Chemistry (2006), 49(6), 1855-1866

CODEN: JMCMAR; ISSN: 0022-2623

PY 2006

L4 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN

TI Anticonvulsant efficacy of the low-affinity partial benzodiazepine receptor agonist ELB 138 in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures

AU Loescher, Wolfgang; Potschka, Heidrun; Rieck, Susanne; Tipold, Andrea; Rundfeldt, Chris

AB Ataxia, sedation, amnesia, ethanol and barbiturate potentiation, loss of efficacy (tolerance), development of dependence, and the potential for drug abuse limit the clin. use of benzodiazepines (BZDs) for long-term treatment of epilepsy or anxiety. BZD ligands that are in current use act as full allosteric modulators of γ -aminobutyric acid (GABA)-gated chloride channels and, on long-term administration, trigger a functional uncoupling between the GABAA and BZD recognition sites. Partial

allosteric modulators, which have a low intrinsic activity at the BZD recognition site of the GABAA receptor, might eventually overcome the limitations of full agonists such as diazepam (DZP). In the present study, the new low-affinity partial BZD-receptor agonist ELB 138 [former name AWD 131-138; 1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one] was evaluated in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures. ELB 138 was shown to increase potently the pentylenetetrazole (PTZ) seizure threshold in dogs. Prolonged oral administration with twice-daily dosing of ELB 138 with either 5 or 40 mg/kg over a 5-wk period was not associated with loss of anticonvulsant efficacy in the PTZ dog model. To study whether phys. dependence developed during long-term treatment, the BZD antagonist flumazenil was injected after 5 wk of treatment with ELB 138. Compared with prolonged treatment with DZP, only relatively mild abstinence symptoms were precipitated in dogs treated with ELB 138, particularly at the lower dosage (5 mg/kg, b.i.d.). In a prospective trial in dogs with newly diagnosed epilepsy, ELB 138 markedly reduced seizure frequency and severity without significant difference to standard treatments (phenobarbital or primidone) but was much better tolerated than the standard drugs. In dogs with chronic epilepsy, most dogs exhibited a reduction in seizure frequency and severity during add-on treatment with ELB 138. The data demonstrate that the partial BZD receptor agonist ELB 138 exerts significant anticonvulsant efficacy without tolerance in a dog seizure model as well as in epileptic dogs with spontaneously recurrent seizures. These data thus substantiate that partial agonism at the BZD site of GABAA receptors offers advantages vs. full agonism and constitutes a valuable approach for treatment of seizures.

SO Epilepsia (2004), 45(10), 1228-1239
CODEN: EPILAK; ISSN: 0013-9580

PY 2004

L4 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI Use of dihydroimidazolones for the treatment of epilepsy in dogs
IN Rundfeldt, Chris; Dost, Rita; Loscher, Wolfgang; Tipold, Andrea;
Unverferth, Klaus; Lankau, Hans-Joachim
AB The invention discloses the use of substituted dihydroimidazolones,
particularly 1-(4-Chlorophenyl)-4-(4-morpholiny)-2,5-dihydro-1H-imidazol-
2-one (AWD 131-138) or a physiol. acceptable
salt thereof for the treatment of epilepsy in dogs.
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2

PY 2004
2005
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2005

L4 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI Evaluation of the novel antiepileptic drug, AWD 131-
138, for benzodiazepine-like discriminative stimulus and
reinforcing effects in squirrel monkeys
AU Yasar, Sevil; Bergman, Jack; Munzar, Patrik; Redhi, Godfrey; Tober,
Christine; Knebel, Norbert; Zschiesche, Michael; Paronis, Carol
AB AWD 131-138 {1-(4-chlorophenyl)-4-morpholino-
imidazolin-2-one}, a new low-affinity partial benzodiazepine receptor
agonist with potent anticonvulsant and anxiolytic properties in rodent
models, was studied in squirrel monkeys trained to discriminate i.m.
injections of midazolam (0.3 mg/kg) from injections of vehicle. Diazepam
produced midazolam-like responding at cumulative doses of 1.0 and 3.0
mg/kg i.m. and decreased rates of responding at 3.0 mg/kg (plasma levels

of about 400 ng/mL). In contrast, AWD 131-138 did not produce midazolam-like responding or alter response rates at cumulative doses up to 18.0 mg/kg i.m. (plasma levels over 2100 ng/mL). Other monkeys were trained to i.v. self-administer cocaine (56.0 µg/kg/injection). When AWD 131-138 (10-100 µg/kg/injection) was studied by substitution, responding declined to vehicle substitution levels within three sessions. At the dose of 100 µg/kg i.v. AWD 131-138, sufficient drug was self-administered during the first session (about 3.5 mg/kg) to produce plasma levels above 1000 ng/mL, yet responding over the next two sessions dropped to vehicle levels. The failure of AWD 131-138 to produce benzodiazepine-like discriminative effects and the absence of drug self-administration behavior when substituted for cocaine suggest that its abuse liability is low.

SO European Journal of Pharmacology (2003), 465(3), 257-265
CODEN: EJPHAZ; ISSN: 0014-2999

PY 2003

L4 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI Analytical data and physicochemical properties of 1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one, AWD 131-138
AU Heinecke, K.; Thiel, W.
AB The structure of the anticonvulsant 1-(4-chlorophenyl)-4-(4-morpholiny)-2,5-dihydro-1H-imidazolin-2-one (Code: AWD 131-138, CAS-Number: 188116-07-6) was proved by IR, UV, 1H NMR, 13CNMR, and mass spectra. AWD 131-138 is practically insol. in a neutral aqueous medium at 20°C (S .apprx. 0.08 g/l). The solubility of the substance in 0.1 N HCl is about 2.7 g/l. In DMF, AWD 131-138 is sparingly soluble (S .apprx. 28.5 g/l). The pKa-value is about 2.5. The partition coeffs. P = COctanol/CWater at 37°C range from 0.7 at pH .apprx. 1 to about 20 at pH ≥6.

SO Pharmazie (2001), 56(6), 458-461
CODEN: PHARAT; ISSN: 0031-7144

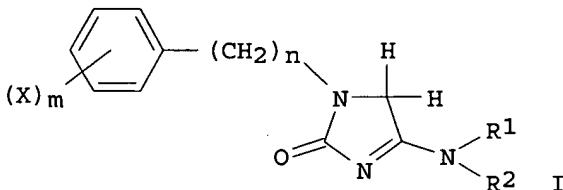
PY 2001

L4 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI An assessment of rufinamide as an anti-epileptic in comparison with other drugs in clinical development
AU Jain, Kewal K.
AB A review with 28 refs. This article evaluates rufinamide, a new anti-epileptic drug (AED) in Phase III development. This review is done against the background of therapeutic challenges of epilepsy, old established AEDs, newly introduced AEDs and AEDs in clin. development. Pharmacol. properties of 12 AEDs in clin. trials (Phases I - III) are compared: ADCI, AWD 131-138, DP-VPA, ganaxolone, levetiracetam, losigamone, pregabalin, remacemide hydrochloride, retigabine, rufinamide, soretolide and TV1901. One of these, levetiracetam has been approved in the USA and is waiting approval in other countries. The protective index of rufinamide, as shown in rodent models of epilepsy, is much higher than that of most common AEDs. Features which make it a desirable AED are: (i) a broad spectrum of anti-epileptic actions including both partial and symptomatic generalized epilepsy; (ii) a statistically significant reduction in seizure frequency in clin. trials; (iii) efficacy and safety shown in a broad range of age groups including children and the elderly; (iv) rapid oral absorption enabling quick titration to ED and (v) a benign adverse event profile. Most of the events did not lead to discontinuation in clin. trials. These features offer considerable advantages over the existing anti-epileptic drugs. It is one of the two drugs in development which have reached Phase III and is expected to be approved by the year 2001 - 2002.

SO Expert Opinion on Investigational Drugs (2000), 9(4), 829-840
CODEN: EOIDER; ISSN: 1354-3784

PY 2000

L4 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI Imidazolinone derivatives for treatment of anxiety and tension
IN Rostock, Angelika; Dost, Rita; Tober, Christine; Bartsch, Reni;
Unverferth, Klaus; Rundfeldt, Chris
GI



AB A process for the treatment of anxiety and tension comprises administering to a patient in need therefor an anxiolytically effective amount of I ($X = H, C1-4$ alkyl, $C1-4$ alkoxy, CF_3 , halo; $R1, R2 = C1-4$ alkyl, cycloalkyl, $C2-4$ hydroxyalkyl, heteroalkyl, or $R1$ and $R2$ together form $C2-6$ alkylene in which one CH_2 can be replaced by O, N, or S; $n = 0, 1$; $m = 0-5$) or a pharmaceutically acceptable salt thereof.
SO U.S., 8 pp.
CODEN: USXXAM
PY 1999
1998

L4 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI New anti-epileptic drugs
AU Walker, Matthew C.; Sander, Josemir W.
AB A review with 78 refs. Epilepsy represents the most common serious neurol. disorder, with a prevalence of 0.4-1%. Approx. 30% of patients are resistant to currently available drugs. New anti-epileptic drugs are needed to treat refractory epilepsy, improve upon current therapies, improve the prognosis of epilepsy and to prevent the epileptogenic process. Designing compds. with specific physiol. targets would seem the most rational method of anti-epileptic drug development, but results from this approach have been disappointing; the widespread screening of compds. in animal models has been much more fruitful. Older methods of animal screening have used acute seizure models, which bear scant relationship to the human condition. More modern methods have included the development of animal models of chronic epilepsy; although more expensive, it is likely that these models will be more sensitive and more specific in determining anti-epileptic efficacy. In this review, we consider the possible physiol. targets for anti-epileptic drugs, the animal models of epilepsy, problems with clin. trials and ten promising anti-epileptic drugs in development (AWD 131-138, DP16 (DP-VPA), ganaxolone, levetiracetam, losigamone, pregabalin, remacemide, retigabine, rufinamide and soretilide). Perhaps the most important advances will come about from the realization that epilepsy is a symptom, not a disease. Preclin. testing should be used to determine the spectrum of epilepsies that a drug can treat, and to direct later clin. trials, which need to select patients based on carefully defined epilepsy syndromes and etiologies. Not only will such an approach improve the sensitivity of clin. trials, but also will lead to a more rational basis on which to treat.
SO Expert Opinion on Investigational Drugs (1999), 8(10), 1497-1510
CODEN: EOIDER; ISSN: 1354-3784
PY 1999

L4 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI Progress report on new antiepileptic drugs: a summary of the fourth Eilat conference (EILAT IV)

AU Bialer, M.; Johannessen, S. I.; Kupferberg, H. J.; Levy, R. H.; Loiseau, P.; Perucca, E.

AB A review with apprx.65 refs. The Fourth Eilat Conference on New Antiepileptic Drugs (AEDs) was held at the Royal Beach Hotel, Eilat, Israel, from 6th to 10th Sept. 1998. Epileptologists and scientists from 20 countries attended the conference, which was held to discuss a number of issues in drug development, including outcome assessment in epilepsy (long-term efficacy, quality of life, safety), cost-effectiveness, an update on drugs in development, a progress report on recently marketed AEDs, and controversies in strategies for drug development. This review focuses on drugs in development and recently marketed AEDs. Drugs in development include ADCI, AWD 131-138, DP16, ganaxolone (CCD 1042), levetiracetam (ucb L059), losigamone, pregabalin (iso-Bu GABA [CI-1008]), remacemide hydrochloride, retigabine (D-23129), rufinamide (CGP 33101), soretonide (D2916), TV1901, and 534U87. New information on the safety and efficacy of recently marketed drugs (felbamate, fosphenytoin, gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide) and of a new antiepileptic device, the neurocybernetic prosthesis (NCP), has become available. This paper summarizes the presentations made at the conference.

SO Epilepsy Research (1999), 34(1), 1-41

CODEN: EPIRE8; ISSN: 0920-1211

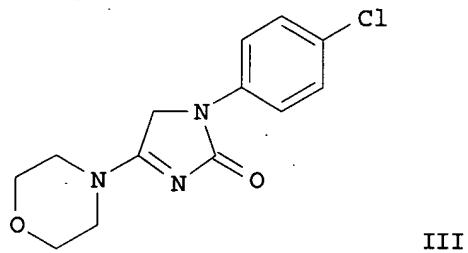
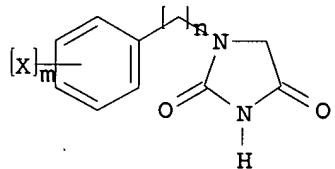
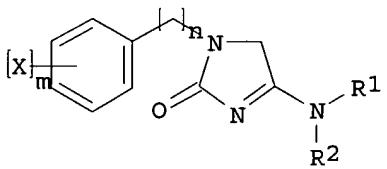
PY 1999

L4 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN

TI Preparation of anticonvulsive 1-ar(alk)ylimidazolin-2-ones

IN Lankau, Hans-Joachim; Menzer, Manfred; Unverferth, Klaus; Gewald, Karl; Schafer, Harry

GI

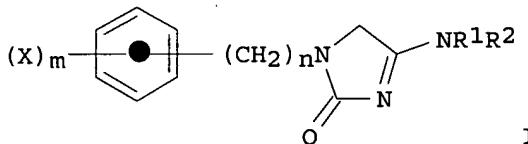


AB The title compds. [I; X = H, C1-4 alkyl, C1-4 alkoxy, etc.; R1, R2 = C1-4 alkyl, C2-4 hydroxyalkyl, C3-10 cycloalkyl; R1R2 = C2-6 alkylene residue in which CH₂ group is optionally replaced by O, N or S; n = 0-1; m = 0-5], useful for treating an epileptic disorders, were prepared by reacting imidazolidinedione II with a secondary amine HNR₁R₂. E.g., the title compound III showed ED₅₀ (p.o) of 21 mg/kg for the maximum electroshock, ED₅₀ of 16 mg/kg in the s.c. pentetetrazole test, and NT₅₀ for neurotoxicity of > 400 mg/kg.

SO U.S., 5 pp., Cont.-in-part of U.S. Ser. No. 708,665, abandoned.
CODEN: USXXAM

PY 1999
1997

L4 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI Use of 1-ar(alk)ylimidazolin-2-ones for treating anxiety and stress
conditions
IN Rostock, Angelika; Dost, Rita; Tober, Christine; Bartsch, Reni;
Unverferth, Klaus; Rundfeldt, Chris
GI



AB The title compds. (I; X = H, C1-4 alkyl or alkoxy, CF3, halo; R1, R2 = C1-4 alkyl, cycloalkyl, heteroalkyl, or R1 and R2 together = C2-6 alkylene in which 1 CH2 group may be substituted by O, N, or S; m = 0-5; n = 0, 1) and their pharmaceutically acceptable salts are effective in treatment of anxiety and stress without sedative side effects. This was demonstrated by the decrease in conflict avoidance behavior in mice induced by 1-(4-chlorophenyl)-4-morpholinoimidazolin-2-one (3-10 mg/kg orally). I showed little pharmacol. interaction with EtOH and little neurotoxicity.

SO Ger. Offen., 10 pp.

CODEN: GWXXBX

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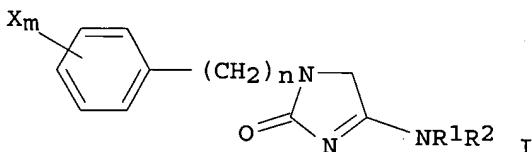
L4 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI AWD 131-138 as anxiolytic anticonvulsant
AU Rostock, A.; Tober, C.; Dost, R.; Rundfeldt, C.; Bartsch, R.; Egerland, U.; Stark, B.; Schupke, H.; Kronbach, T.; Lankau, H. -J.; Unverferth, K.; Engel, J.
AB A review with 3 refs. on the synthesis and pharmacol. of the title anticonvulsant.

SO Drugs of the Future (1998), 23(3), 253-255
CODEN: DRFUD4; ISSN: 0377-8282
PY 1998

L4 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI The antiepileptic drug AWD 131-138
stimulates different recombinant isoforms of the GABAA receptor through
the benzodiazepine binding site
AU Sigel, Erwin; Baur, Roland; Netzer, Rainer; Rundfeldt, Chris
AB Recombinant γ -aminobutyric acid A (GABAA) receptors of the subunit
compns. $\alpha_1\beta_2\gamma_2$, $\alpha_1\beta_3\gamma_2$,
 $\alpha_2\beta_2\gamma_2$, $\alpha_3\beta_2\gamma_2$ and
 $\alpha_5\beta_2\gamma_2$ were expressed in Xenopus oocytes in a
functionally active form. At all subunit combinations, AWD
131-138 dose-dependently stimulated GABA currents. At
10 μ M AWD 131-138, this allosteric
stimulation amounted in average to about 12-21% of the maximal stimulation
achieved using diazepam. The threshold of stimulation was about 0.3-1.0
 μ M. One micrometer of the benzodiazepine antagonist flumazenil (Ro
15-1788) counteracted the current stimulation by 10 μ M AWD
131-138, indicating that this drug acts at the binding
site for benzodiazepines.

SO Neuroscience Letters (1998), 245(2), 85-88
CODEN: NELED5; ISSN: 0304-3940
PY 1998

L4 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of 4-amino-1-aralkylimidazolones as anticonvulsants.
IN Lankau, Hans-Joachim; Menzer, Manfred; Unverferth, Klaus; Gewald, Karl;
Schaefer, Harry
GI



AB Title compds. [I; X = H, alkyl, alkoxy, CF3, halo; R1, R2 = alkyl,
cycloalkyl, heteroalkyl; R1R2 = alkylene optionally interrupted by O, N,
or S; n = 0, 1; m = 0-5], were prepared Thus, 1-(4-chlorophenyl)-4-
piperidinoimidazolin-2-one (general preparative methods given) at 100
mg/kg in rats gave 100% inhibition of maximal electroshock-induced
convulsions.

SO Ger. Offen., 7 pp.
CODEN: GWXXBX

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